UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,023	01/19/2000	Parkash S. Gill	21327-701 CIP	2622

7590 11/19/2003

McCutchen Doyle Brown & Enersen LLP
Three Embarcadero Center
San Francisco, CA 94111

EXAMINER	
MCGARRY, SEAN	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/487,023	GILL ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12 and 16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 January 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/8/2003 has been entered.

Claims 2-9, 11 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites "in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293" This limitation is found to be vague and indefinite since there is no basis for what this numbering is based on. One in the art would not know what specifically is included in the recited range without being provided a basis for that range in the claim, for example.

Claims 2 and 17 recite "selected from among SEQ ID NOS: . . ."; claim 7 recites "chosen from among SEQ ID NOS: . . ."; and claim 19 recites "has a sequence shown in one of among SEQ ID NOS: . . .". It is unclear what the claims are intended to encompass. The use of the term among in the instant claims provides for ambiguity in the formally clear Markush language of the claims. With the use of the term "among" it is

not clear whether one would select from the "group consisting of", as the claims clearly recited before amendment, or whether one in the art would select an oligonucleotide or sequence from the class defined by the recited oligonucleotides, for example. The recited oligonucleotides as a group or class all over lap and define a target region of VEGF such a region defined by nucleotides 259-293, for example (see applicants specification at Figure 1). (See The American Heritage Dictionary of the English Language definition for among). In claim 19, for example is one selecting a sequence from within of the SEQ IDs or is one to chose one of the specified SEQ IDs?

Claims 2, 3, 9, 11, 16, 17-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Uchida et al [US 6,150, 092]. See rejection under 35 U.S.C. 112, second paragraph above. This rejection is applied as the invention is interpreted to read on antisense to a target region, for example.

Uchida et al disclose many antisense oligonucleotides that are targeted to the same target region those antisense disclosed in the instant specification and embraced in the instant claims and it is assumed that the antisense of Uchida et al inherently posses the ability to inhibit at the conditions recited in the claims without evidence to the contrary. See Tables 1 and 2, for example. All of the specifically recited antisense oligonucleotides of instant claim 2, for example, are all targeted to the same region as SEQ ID NO: 7 of Uchida et al, and further many of the recited antisense oligonucleotides of instant claim 2 either overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 51,

54, 53, 50, 49, 138, and 141 of Uchida et al, for example appl). Uchida et al further claim antisense targeted to the region of SEQ ID NO: 7 (see claim 2-4, for example). Uchida et al disclose liposomes at column 9, for example. Uchida et al further disclose pharmaceutical preparations for treatment of disease throughout their specification and claims. At columns 4 and 8-9 of Uchida et al, for example, pharmaceutical compositions and methods of treatment with phosphorothioate linkages are disclosed. The prior art therefore teaches the structural limitations of the claimed invention and further demonstrates that many of those instantly claimed overlap, embrace or are embraced by those antisense taught in the art where all of these antisense are targeted to the same region defined by SEQ ID NO:7 of Uchida et al which region is a relatively small region of under 50 nucleotides. Applicants claim limitations of a particular IC_{50} is not seen as providing a difference between the prior art antisense and that instantly claimed since no particular conditions for the cell cultures in the determination of such a value are required by the claims. This allows one in the art to set the conditions such that a particular IC50 value may be observed.

A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION,AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." Th burden of proof is similar to that required with r spect to pr duct-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

MPEP 2112.01:

PRODUCT AND APPARATUS CLAIMS – WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

COMPOSITION CLAIMS - IF THE COMPOSITION IS PHYSICALLY THE SAME, IT MUST HAVE THE SAME PROPERTIES

"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)

Claims 2, 3, 9-12, and 16-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al (above) and Robinson et al [5,814,620; 5,710,136; and, 5,801,156].

The claimed invention is antisense oligonucleotides for the inhibition of VEGF where there are several specific antisense sequences, all targeted to a region of 34 nucleotides, recited in the claims.

Uchida et al have taught methods of inhibiting VEGF with antisense oligonucleotides. The antisense oligonucleotides claimed by Uchida et al are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. All of the specifically recited antisense oligonucleotides of instant claims 2, 10, 12, 17 and 19, for

example, are all targeted to SEQ ID NO: 7 of Uchida et al., which region is relatively small at 42 nucleotiodes in length. Further, many of the recited antisense oligonucleotides of instant claims 2, 10, 12, 17 and 19 overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al, for example). Uchida et al have taught that the region defined by SEQ ID NO:7, to which all of the claimed oligonucleotides are targeted, is a desirable region to target and is even referred to as a "core region" for targeting VEGF with antisense. Uchida et al further disclose pharmaceutical preparations for treatment of disease throughout their specification and claims. At columns 4 and 8-9 of Uchida et al, for example, pharmaceutical compositions and methods of treatment with phosphorothioate linkages are disclosed.

Robinson et al, in all of the three cited references, has demonstrated that antisense oligonucleotides targeted to VEGF have been known for use in various methods of treatment prior to applicants invention. It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier.

Applicants claim limitations of a particular IC_{50} is not seen as providing a difference between the prior art antisense and that instantly claimed since no particular conditions for the cell cultures in the determination of such a value are required by the claims. This allows one in the art to set the conditions such that a particular IC50 value may be observed.

One in the art would clearly have had motivation to make the instantly claimed antisense molecules since it is absolutely clear that the region targeted has been clearly shown by the prior art to be a desired target for antisense inhibition of VEGF. Furthermore the specific antisense claimed are not only targeted to the taught target sequence but many overlap, embrace or are embraced by the specific VEGF antisense taught by Uchida et al. One in the art would clearly look to these specific regions to make antisense oligonucleotides to inhibit VEGF since the specific region has clearly been shown to be an effective target region and antisense to this target have been clearly taught in the art to be effective antisense oligonucleotides. One in the art would clearly look to the region taught by Uchida to be a "core region" for antisense targeted to VEGF to optimize antisense targeted to VEGF, for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al., Robinson et al [US 5,814,620], Barleon et al [Blood Vol. 87, No. 8:3336-3343, 4/15/96] and Chan et al [The American journal of Surgical Pathology Vol. 22(7):816-826, 1998].

Uchida et al is relied upon as above and further for the following: It has been taught at column 1, for example, that ". . .inhibition of the vascular endothelial growth factor leads to inhibition of growth of solid tumor cells, and this should be applicable in

the development of anticancer agents. [I]n fact there is a report on a method to use an anti-VEGF antibody"

Robinson et al has demonstrated that antisense oligonucleotides targeted to VEGF have been known for use in various methods of treatment prior to applicants invention and that it was known to use liposome formulations for pharmaceutical preparations of antisense oligonucleotides (see column 9, for example). It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier. It is further taught that such compositions can include other factors and/or agents which enhance inhibition of VEGF expression or which will reduce neovascularation (see columns 8 and 9, for example). It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier. It is further taught that such compositions can include other factors and/or agents which enhance inhibition of VEGF expression or which will reduce neovascularation (see columns 8 and 9, for example).

Barleon et al taught inhibition of VEGF via specific antiserum and the role of flt-1 with VEGF biopathway.

Chan et al have taught the Association of VEGF and its receptors and their roles in various diseases.

Applicants claim limitations of a particular IC_{50} is not seen as providing a difference between the prior art antisense and that instantly claimed since no particular

conditions for the cell cultures in the determination of such a value are required by the claims. This allows one in the art to set the conditions such that a particular IC50 value may be observed.

It would have been obvious to use antibodies in conjunction with antisense targeted to VEGF since the prior art has taught antisense to inhibit VEGF, antibodies to inhibit VEGF and since the art has taught that VEGF receptors are associated with the same disease sates as VEGF. The art has taught that one in the art can combine other VEGF inhibitors in combination with VEGF antisense. Since the art has shown inhibition of VEGF by antisense and via antibodies one in the art would have a reasonable expectation of the successful use of a combination of such a combination and further to simply combine different antisense targeted to the same target, for example. Furthermore it is prima facie obvious to combine two composition each of which has been taught in the art to be useful for the same purpose (see MPEP2144.06, for example).

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Applicant's arguments filed 8/8/2003 have been fully considered but they are not persuasive.

Applicant argues that new claims 16-19 are not anticipated since Uchida does not provide any reliable direction as to which antisense they disclose would be useful

when formulated for use in a human. Applicant is directed to claims 5, 6 and 18-20, and columns 4 and 8-9 of Uchida et al, for example where pharmaceutical compositions and methods of treatment are claimed and pharmaceutical compositions and methods of treatment with phosphorothioate linkages are disclosed. Clearly Uchida et al provide ample guidance for the use of VEGF antisense in pharmaceutical compositions.

Applicant argues that the specifically recited oligonucleotides are not obvious. Applicant requests that the examiner refrain from ad hoc comments on the patentability of unclaimed embodiments. It is noted that the comments of the examiner are directed to those embodiments specifically claimed and those embraced within the scope of the claims. The examiner clearly would not wish to waste applicants or his time with rejecting inventions not claimed. If applicant believes such rejections have beeen made applicant is invited to specifically point out where such rejections have been made so that the examiner may refrain from such rejections if such rejections have been made. Applicant asserts that the region taught by Uchida would not provide an art recognized meaningful predictive value. Applicant referes to an "Exhibit 1" Agrawal et al [PNAS USA 94:2620-2625] in support of this argument. There has been no submission of this reference and that which was submitted and clearly marked as "EXHIBIT 1" is Matveeva et al NAR Vol. 28, N0. 15: 2862-2865, 2000. Neither reference has been considered. Applicant should provide these references in a properly filed IDS with the appropriate fee so that they may be properly considered. Applicant then argues "GC" content calculations. The examiner declines further checking of the simple, yet laborious calculations of applicant since, applicant has not provided the calculations to be

checked and further since the argument of the GC content of the oligonucleotide of Uchida is greatly off point. Applicant compares apples and oranges. Why has applicant not considered only those oligonucleotides of Uchida et al that are targeted to the same region as those instantly claimed? Since both are targeted to substantially the same region it appears only logical to make such a comparison instead of applicants comparison of all of the oligonucleotides of Uchida et al targeted to the entirety of VEGF and compare those to applicants which are targeted to a region of only tens of nucleotides. It would seem to one of ordinary skill in the art that the target sequence would dictate the GC content of the oligonucleotides targeted thereto, especially when the target region is a small as in the instant invention and that taught by Uchida et al. Applicant argues that Uchida's cell-free assay was nearly useless as a predictor of effectiveness in a cellular setting. This position is confusing since Uchida's methods show that the region defined by SEQ ID NO: 7 was a core region desirable for targeting antisense and this same region is where applicants target antisense. Applicant argues that the effectiveness of Uchida's SEQ ID NO: 51 and 47 as phosphorothioates. Again it is unclear what is applicants point. The antisense work. Applicant has not shown that their antisense under the same conditions as Uchida, function unexpectedly better or that Uchida's under those of applicants are unexpectedly poor, for example. Applicant attacks the methods of Uchida, but fails to specifically point out how each and every "shortcoming in Uchida" is avoided or addressed by applicant own disclosure. Applicant argue phosphorothioate of Uchida et al but applicants specification fails to show the activity of all of their oligonucleotides in an unmodified state, for example. Clearly one in

the art would have looked to the region disclosed by Uchida et al to optimize antisense targeted to that same region. Applicant again is directed to the following.

> **A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION,AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE**
>
> **"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).**
>
> **MPEP 2112.01:**
>
> **PRODUCT AND APPARATUS CLAIMS — WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT**
>
> **Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.**
>
> **COMPOSITION CLAIMS - IF THE COMPOSITION IS PHYSICALLY THE SAME, IT MUST HAVE THE SAME PROPERTIES**
>
> **"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)**

Based on the disclosure and teachings of the prior art and the cites above it is clear that the burden was properly shifted to applicant after the mailing of the Official Action mailed 5/17/02. It is applicants burden to provide evidence of an unobvious difference between the prior art and that instantly claimed. It is noted that applicant has

asserted that they reserve the right to later present comparative data to overcome an inherency rejection. It is noted that applicant may provide such data in response to the instant Official Action, however, no such data will be considered after a final rejection in the instant application unless accompanied by a request for continued examination.

Any rejection previously made and not maintained in the instant Official Action is withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703)305-7028. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SRM

SEAN McGARRY
PRIMARY EXAMINER
1635